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ORIGINAL ARTICLE

Investigation of the Lipid-Modifying and Antiinflammatory Effects of *Cornus mas* L. Supplementation on Dyslipidemic Children and Adolescents

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Abstract *Cornus mas* L. (CM) fruits are rich in anthocyanins and possess both antiinflammatory and antioxidant activities. The current study was conducted to investigate whether supplementation with CM could ameliorate lipid profile and vascular inflammation in dyslipidemic children and adolescents. In this randomized clinical trial, 40 dyslipidemic children and adolescents ages 9 to 16 years were assigned to receive 50 g of CM twice a day after lunch and dinner ($n = 20$, case group) or to continue their normal diet ($n = 20$, control group). The serum levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), apo A-I, apo B, intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), C-reactive protein (CRP), and anthropometric indices were determined at baseline and then after weeks 3 and 6 of the trial. After week 6 of the trial, the TC, TG, LDL-C, apo B, ICAM-1, and VCAM-1 levels in the CM group were significantly lower and the HDL-C and apo A-I levels higher than at baseline. After week 6 of the trial, none of these parameters in the control group, except for ICAM-1, was significantly altered from baseline. However, between-group comparison showed a significant difference only for apo A-I ($p = 0.016$) and a borderline significant difference for ICAM-1 ($p = 0.076$). No significant difference in body mass index, waist-to-hip ratio, or C-reactive protein was observed between the studied groups. The present findings revealed a trend toward amelioration of lipid profile and vascular inflammation following addition of CM to the daily diet of dyslipidemic children and adolescents but this needs to be verified by larger scale trials.

Keywords Adolescent · Atherosclerosis · Children · Cornelian cherry · *Cornus mas* L. · Dyslipidemia

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Introduction

The prevalence of dyslipidemia is increasing worldwide [35], and this trend is closely associated with a rise in atherothrombotic events such as cardiovascular and cerebrovascular diseases. Both of these diseases are among the leading causes of death and disability in industrialized countries [15].

Atherosclerosis is the underlying cause of coronary heart disease (CHD), which starts from childhood and progresses over time in a chronic and silent fashion [24]. Observational studies have consistently indicated that dyslipidemia can impair vascular integrity, structure, and function in children [38]. Anatomic evidence from population studies has shown that cardiovascular risk factors,

when present in childhood, have a detrimental impact on the vascular endothelium and accelerate disease progression during childhood and adulthood [19]. In most children, atherosclerotic vascular changes are minor and can be minimized or prevented with a healthy lifestyle [2].

The use of plants as medicines dates back to the earliest years of human life. Consumption of fruits, particularly those with higher contents of phenolics and flavonoids, has been shown to ameliorate lipid profile status and to be inversely associated with the incidence of cardiovascular disease [23, 44]. Fruits of the Cornelian cherry (*Cornus mas* L. [CM]) are characterized by a high nutritional value [1]. Moreover, CM has been used in the traditional medicine of the Caucasus and Central Asia for more than 1,000 years. Traditional applications of CM include treatment of diarrhea, inflammatory bowel disease, fever, malaria, kidney stones, urinary tract infections, cancer, and sunstroke [43].

Cornus mas L. is a rich source of several bioactive phytochemicals including anthocyanins, ursolic acid, and vitamin C [16, 33, 37, 39]. Anthocyanins such as cyanidin, malvidin, peonidin, pelargonidin, and petunidin are endowed with a multitude of pharmacologic properties including lipid-lowering, antioxidant, anti-allergic, antiinflammatory, anticoagulant, and antidiabetic effects [3, 9, 12, 16, 37, 39]. Considering the rich content of anthocyanins and other phytochemicals with cardioprotective, antiinflammatory, and lipid-lowering properties in CM, this plant can potentially ameliorate dyslipidemia and vascular inflammation. The current study was undertaken to verify this hypothesis in a randomized trial among dyslipidemic children and adolescents.

Methods

Participants

This randomized clinical trial was designed to evaluate the antidyslipidemic and antiinflammatory effects of CM on children. The study, conducted in 2011, recruited 40 dyslipidemic children ranging in age from 9 to 16 years. The participants were randomly selected from those referred to the Pediatric Preventive Cardiology Department of the Isfahan Cardiovascular Research Center affiliated within the Isfahan University of Medical Sciences (Isfahan, Iran). The allocation was conducted with computer-generated random numbers using the participants' record numbers in the clinic.

The inclusion criteria were patients 9 to 16 years of age who had at least one of the following dyslipidemic measures: serum TG $\geq$ 150 mg/dL, TC $\geq$ 170 mg/dL, LDL-C $\geq$ 130 mg/dL or HDL-C $<$ 35 mg/dL. The exclusion criteria ruled out the use of medications altering lipid metabolism; subjects with known chronic diseases such as diabetes mellitus, nephrotic syndrome, and chronic pancreatitis; and liver, thyroid, and bile duct disorders.

The demographic and medical histories were taken from the reports of participants and their parents. The study protocol was approved by the Medical Ethics Committee of the Isfahan Cardiovascular Research Center under approval no. 89108.

Study Design

Cornus mas L. fresh fruits were purchased from a local fruit market in Isfahan, Iran. The genus and species of each plant were identified and authenticated by a plant taxonomist and deposited with the herbarium code of 093/001/001 at the Isfahan Department of Natural Resources.

The participants were randomized into two groups of equal size ($n = 20$). The participates in the two groups were matched for age, sex, height, and weight. Both groups received similar advice on physical activity and diet during the course of the study. The case group was administered 50 g of CM twice a day after lunch and dinner for a period of 6 weeks.

Biochemical and Anthropometric Measurement

All measurements were made by a trained team of general physicians and nurses under the supervision of the same pediatrician. Anthropometric and biochemical measurements were performed using calibrated instruments and standard protocols at baseline and then after weeks 3 and 6 of the trial.

Fasting venous blood samples were collected from both groups for measurement of the biochemical factors. Serum total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) levels were assayed using Pars Azmoon kits (Iran) on a Hitachi auto-analyzer (Japan). Low-density lipoprotein cholesterol (LDL-C) values were calculated according to the Friedewald formula [11]. Apolipoproteins (apo A-I and apo B) and C-reactive protein (CRP) concentrations were determined using Pars Azmoon kits (Pars Azmoon Co., Tehran, Iran) on an automated chemistry analyzer (Hitachi model 902) (Hitachi Ltd., Tokyo, Japan) and based on a turbidimetric method. Serum concentrations of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) were determined using an enzyme-linked immunoassay (ELISA) (Boster Biological Technology Ltd., Wuhan, China).

Waist circumference was determined from the point halfway between the lower border of ribs and the iliac crest in a horizontal plane. Body mass index (BMI) was calculated by dividing weight (in kilograms) by height (in square meters), and the waist-to-hip ratio (WHR) was calculated by dividing waist circumference (cm) by height (in centimeters).

Statistical Analysis

Data are expressed as means ± standard deviations. Statistical analyses were performed using SPSS program, version 16.0 (SPSS, Chicago, IL, USA).Independent samples *t*-tests and paired samples *t*-tests were applied to compare group means. The efficacy of CM to improve anthropometric, lipid profile, and inflammatory factors was assessed using repeated measures analysis of variance (ANOVA). A p value lower than 0.05 was considered to be statistically significant.

Results

Changes in anthropometric parameters (BMI and WHR) during the 6-week course of the trial were comparable between the CM and control groups ($p > 0.05$) (Table 1). Overall, there were significant reductions in TC, TG, and LDL-C, and significant increases in HDL-C, HDL-C/TC, and HDL-C/LDL-C from baseline to week 6 in the CM group ($p < 0.05$). The posttrial values for these parameters after week 6 were statistically unchanged compared with the baseline values in the control group ($p > 0.05$). Nonetheless, between-group differences did not reach statistical significance ($p > 0.05$) (Table 2).

Similar to lipoproteins, analysis of apolipoproteins showed a significant elevation of apo A-I and a decline in apo B after CM consumption ($p < 0.05$). However, the magnitude of the changes reached statistical significance only for apo A ($p = 0.016$) (Table 3).

With regard to the inflammatory biomarkers, significant reductions in ICAM-1 and VCAM-1 were observed in the CM group after week 6 compared with baseline ($p < 0.05$), whereas no significant alteration was observed for serum CRP ($p > 0.05$). The magnitude of the changes in the aforementioned parameters were not found to differ significantly between the groups, although a trend toward superiority of CM was observed for ICAM-1 ($p = 0.076$) (Table 4).

Discussion

Evidence from the current trial indicated a trend toward improvement of the lipid profile (comprising LDL-C, HDL-C, TC, TG, apo A-I, and apo B) and the vascular inflammation biomarkers (ICAM-1 and VCAM-1) after CM consumption. Although most of these parameters remained statistically unchanged in the control group, we failed to detect a significant between-group difference between the studied arms. This issue could be attributable to the relatively few recruited subjects and associated limited power as well as the short supplementation period.

Dyslipidemia is an important risk factor for cardiovascular and cerebrovascular disease and associated complications [15]. Phenolics, particularly flavonoids, are natural products that constitute an important part of the human diet and are considered to be active constituents in many medicinal plants [4, 8, 10, 18, 25, 28, 29, 32]. Hence, a great deal of interest has been focused on identifying bioactive flavonoids from natural sources to be exploited for pharmacologic and medicinal properties.

A study by Rafieian-Kopaei et al. [30] found that daily supplementation with 1 g/kg bodyweight of CM powder in hypercholesterolemic rabbits for 60 days was associated with a significant increase in the atherogenic index (log TG/HDL) of plasma. Additionally, CM decreased TC, LDL, and TG levels together with atherosclerotic lesion in the aorta, although these reductions were not statistically significant.

Anthocyanin-rich diets such as those containing cherries show evidence of an impact on the modulation of dyslipidemia through reducing TC, TG, glucose, insulin, and liver fat levels [7]. Seymour et al. [34] reported that cherry-enriched diets significantly lowered plasma TC and TG while slightly raising HDL-C and significantly elevating plasma antioxidant capacity. The cherry-enriched diets also showed an interesting antisteatotic effect due to the mitigation of TG and cholesterol accumulation in the liver.

Table 1 Effect of *Cornus mas* on body mass index (BMI) and waist-to-hip ratio (WHR) levels in experimental groups

	Group	Baseline	Week 3	Week 6	Interaction p value time × group	Group p value	Time p value
Mean BMI	Control	24.07 ± 2.34	24.14 ± 2.39	24.30 ± 2.18[a]	0.253	0.513	0.624
	Case	25.16 ± 4.56	25.05 ± 4.38	25.06 ± 4.49			
	p value	0.19	0.24	0.65			
Mean WHR	Control	0.91 ± 0.03	0.91 ± 0.03	0.91 ± 0.03	0.688	0.425	0.879
	Case	0.92 ± 0.03	0.92 ± 0.03	0.92 ± 0.03			
	p value	0.69	0.74	0.43			

[a] Significant difference versus baseline

Table 2 Effect of *Cornus mas* on lipid profile levels in experimental groups

Lipid profile	Group	Baseline	Week 3	Week 6	Interaction *p* value time × group	Group *p* value	Time *p* value
Total cholesterol (TC) (mg/dL)	Control	205.72 ± 34.75	208.83 ± 34.10	199.44 ± 34.95	0.033	0.599	0.001
	Case	225.85 ± 56.02	211.85 ± 53.07[a]	197.14 ± 40.10[a,b]			
	p value	0.435	0.861	0.851			
Triglyceride (TG) (mg/dL)	Control	143.94 ± 49.16	198.61 ± 80.13[a]	154.27 ± 53.04[b]	0.057	0.100	0.006
	Case	137.38 ± 46.51	140.14 ± 37.78	120.47 ± 50.56[a,b]			
	p value	0.416	0.005	0.049			
Low-density lipoprotein (LDL) (mg/dL)	Control	211.33 ± 38.58	205.05 ± 43.41	205.81 ± 42.09	0.234	0.559	0.015
	Case	229.00 ± 57.28	212.45 ± 59.10[a]	206.20 ± 39.78[a]			
	p value	0.601	0.956	0.721			
High-density lipoprotein (HDL) (mg/dL)	Control	34.44 ± 14.74	35.94 ± 10.42	37.22 ± 11.03	0.166	0.397	0.003
	Case	30.70 ± 12.07	30.30 ± 12.61	36.85 ± 14.51[a,b]			
	p value	0.170	0.054	0.891			
HDL/TC	Control	0.169 ± 0.07	0.174 ± 0.05	0.190 ± 0.06	0.089	0.343	0.000
	Case	0.141 ± 0.06	0.147 ± 0.05	0.194 ± 0.06[a,b]			
	p value	0.124	0.049	0.829			
HDL/LDL	Control	0.161 ± 0.05	0.178 ± 0.05[a]	0.183 ± 0.05[a]	0.070		
	Case	0.136 ± 0.05	0.143 ± 0.04	0.179 ± 0.05[a,b]	0.180		
	p value	0.103	0.013	0.847	0.000		

Values are expressed as mean ± standard deviation

[a] Significant difference versus baseline

[b] Significant difference versus 3rd week

Table 3 Effect of *Cornus mas* on apo lipoprotein A and B levels in experimental groups

	Group	Baseline	Week 3	Week 6	Time × group interaction *p* value	Group *p* value	Time *p* value
Apo A-I (mg/dL)	Control	150.46 ± 13.12	146.26 ± 9.92[a]	142.46 ± 17.51	0.00	0.016	0.116
	Case	151.33 ± 20.48	158.73 ± 15.03	168.93 ± 17.34[a,b]			
	p value	0.89	0.01	0.00			
Apo B (mg/dL)	Control	78.60 ± 22.48[b]	77.53 ± 22.66[a]	72.46 ± 23.86	0.26	0.619	0.001
	Case	86.93 ± 27.48	78.80 ± 23.40	75.13 ± 19.89[a]			
	p value	0.371	0.881	0.742			

Values are expressed as mean ± standard deviation

[a] Significant difference versus baseline

[b] Significant difference versus 3rd week

Xia et al. [40, 41], reported that diets of atherosclerosis-prone mice supplemented with an anthocyanin-rich extract from black rice significantly reduced atherosclerosis burden, TC and TG concentrations, and tissue cholesterol content while boosting HDL-C levels. According to another study by Jayaprakasam et al. [16], anthocyanin-treated mice exhibited reduced lipid accumulation in the liver, which is particularly important for TG due to its key role in triggering fatty liver disease.

Antioxidants reduce the activity of free radicals and prevent lipid peroxidation [14]. It may be postulated that the beneficial anti-atherosclerotic and antidyslipidemic effects of CM are, at least in part, due to its antioxidant activity [22]. Results by Safari and Sheikh [31] have indicated that phenolic compounds such as quercetin found in tart cherries protect LDL from oxidative damage, thus reducing its atherogenicity. Flavonoids also can protect endothelial cells against oxidative stress and inhibit the

Table 4 Effect of *Cornus mas* on inflammatory factors levels in experimental groups

Inflammatory factors	Group	Baseline	Week 3	Week 6	Interaction *p* value time × group	Group *p* value	Time *p* value
C-reactive protein (mg/L)	Control	1.64 ± 1.86	1.90 ± 1.91	1.72 ± 1.91	0.878	0.954	0.541
	Case	1.72 ± 1.31	1.84 ± 1.43	1.81 ± 1.41			
	p value	0.90	0.915	0.88			
Vascular cell adhesion molecule-1 (ng/mL)	Control	1,176.38 ± 456.09	1,256.98 ± 545.94	1,252.98 ± 453.91	0.112	0.415	0.355
	Case	1,275.35 ± 579.70	1,135.387 ± 322.94	948.23 ± 371.26[a]			
	p value	0.60	0.46	0.054			
Intracellular adhesion molecule-1 (ng/mL)	Control	105.75 ± 20.04	101.086 ± 25.41	97.23 ± 21.24[a]	0.29	0.076	0.000
	Case	105.67 ± 23.16	89.63 ± 21.09	73.84 ± 16.97[a]			
	p value	0.99	0.19	0.02			

Values are expressed as mean ± standard deviation

[a] Significant difference versus baseline

proinflammatory response that usually underlies the process of atheromatous lesion formation [5, 42].

To date, several studies have shown that consumption of flavonoid- and anthocyanin-rich diets helps to lower LDL-C and TG levels and that this effect might be secondary to reduced secretion of apo B-100 and very-low-density lipoprotein (VLDL) packaging [45]. Besides, phenolic acids such as gallic acid have been reported to enhance the expression of LDL receptor and apo B-100 in hepatocytes [6]. Finally, diets rich in anthocyanins and other types of phenolics are known to protect against insulin resistance and obesity, which are common features in the ethiopathogenesis of type 2 diabetes, metabolic syndrome, and fatty liver disease [36].

Vascular inflammation, a primary event in the pathogenesis of atherosclerosis [20], usually is characterized by overexpression of CRP and cellular adhesion molecules such as VCAM-1 and ICAM-1 [21, 27]. A large body of data has indicated the protective effects of flavonoids against vascular inflammation. These protective effects are exerted via different mechanisms including scavenging of reactive oxygen species, upregulation of antioxidant enzymes, downregulation of inflammatory transcription factors and cytokines, amelioration of endothelial function, and enhancement of nitric oxide (NO) bioavailability [13]. In addition, anthocyanins and fruit juices rich in these phytochemicals can interact with CAMs, suppress the tumor necrosis factor-alpha (TNFα)-induced expression of VCAM-1, and downregulate both the surface expression and the release of ICAM-1 [5, 17, 26].

Study Limitations

The current study was limited in a number of ways that deserve careful attention: First, the study population was relatively small, and this could be regarded as the main reason why significant between-group differences for many of the biochemical parameters assessed in this study were not detected. Second, the current trial was subject to potential bias due to the lack of blinding and placebo controlling. Third, the supplementation period in the current trial was 6 weeks. This period may not have been sufficient for detection of significant differences in the circulating levels of lipoproteins and inflammatory factors. Finally, it would be ideal to standardize CM intake based on phytochemicals such as anthocyanins and flavonoids rather than on crude fruit weight. To this end, it is necessary to undertake phytochemical analysis of CM fruit.

Conclusions

In summary, findings from the current trial showed a trend toward amelioration of lipid profile, apolipoprotein status, and vascular inflammation. These findings provide additional evidence for the cardiovascular health benefits of *Cornus* spp. Future large-scale trials are warranted to verify the current findings in larger populations and over longer periods of supplementation.

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Ethical Standard The study protocol was approved by the Medical Ethics Committees of the Isfahan Cardiovascular Research Center under the approval no. 89108

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